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⑭発明の名称　軟カプセル剤

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明　細　書

1．発明の名称

軟カプセル剤

2．特許請求の範囲

1）天然水溶性高分子、親水性物質を天然油中に配合して成る軟カプセル剤。

2）親水性物質として、甘草エキスを必須成分とする請求項1記載の軟カプセル剤。

3）天然油が動物油、植物油および動植物由来の油から選ばれる請求項1記載の軟カプセル剤。

4）該天然水溶性高分子に有機酸及びまたはその塩を配合してなる請求項1記載の軟カプセル剤。

3．発明の詳細な説明

〔産業上の利用分野〕

本発明は合成保存剤や合成乳化剤を一切使用することなく天然物で構成され、親水性の強い物質を含有する医薬品、食品分野等に有用な軟カプセル剤を提供するものである。

〔従来の技術〕

従来、医薬品、化粧品、食品等を液状、ペースト状、懸濁状もしくは粉末状等の形で種々の物質がカプセルに充填するかあるいはカプセル基剤で被覆成形されたカプセル剤が用いられている。親水性や吸湿性の強い物質等を軟カプセル剤に充填する場合、合成乳化剤が添加されている。

〔発明が解決しようとする課題〕

しかしながら、軟カプセル剤に充填することのできるカプセル内容物には制限がある。親水性ないし吸湿性のある植物エキスや薬剤等を軟カプセル剤に充填することが困難である。

すなわち軟カプセル剤のカプセル皮膜剤（基剤）は一般的に水に可溶なゼラチンが主成分であるため、カプセル皮膜剤が溶解したり軟化する様なカプセル内容物を充填することは困難であった。即ち親水性の強い物質等を軟カプセル剤に充填した場合、内容物自体の水分がカプセル皮膜剤側に移行しカプセル皮膜剤を溶解したり変形する。親水性物質等の水分を除去しても軟カプセル皮膜剤を透過する水分により軟カプセル皮膜を軟化するためカプセル皮膜剤を厚くする必要がある。親水

性物質等を軟カプセル剤に充填する場合、例えば小麦胚芽油で内容物の溶出を防ぐためにカプセル皮膜剤の固形分を高くしなければならない。

内容物の固形分を高くすると充填時の流動特性が低下し作業性が悪くなる。

これらのため軟カプセル剤の製造コストが高くなりまた、カプセル皮膜剤を厚くするためカプセルの崩壊性を低下する欠点もある。

また、親水性物質等を軟カプセル剤皮膜剤に充填する場合には、親水性物質等に油成分を乳化ないし懸濁するためにグリセリン脂肪酸エステル、プロピレングリコール脂肪酸エステル、ソルビタン脂肪酸エステル等の合成乳化剤（界面活性剤）が使用されている。今日の社会情勢が健康、自然指向であり、これらの合成乳化剤に対する危惧、不安が高まり現状にそ供合ないものである。

〔課題を解決するための手段〕

本発明は、前記目的を達成する手段を種々検討した結果、親水性物質に天然水溶性高分子を分散溶解した組成物に天然油成分を配合することで、カプセル皮膜剤の変形したり溶解することがない軟カプセルを見出し、本発明を完成した。

親水性物質である甘草エキスを必須成分とし、これに天然水溶性多糖類と有機酸及びまたはその塩を配合することで流動性に優れかつ、水分の移動することがないゲル組成物を得た。このゲル組成物に天然油成分を添加し、乳化組成物を軟カプセル皮膜剤に充填した。

本発明の天然水溶性高分子は、ゲル化性、増粘安定性等の作用を保持している物であれば特に限定されない。

例えば、海藻粘物質であるカラギーナン、ファーセルラン、寒天、アルギン酸等であり、植物性水溶性高分子としては、グアガム、タマリンドウ、ローカストビーンガム、アラビアガム、ペクチン、デンプン、デキストリン、コンニャクマンナン等であり、微生物生産粘質水溶性高分子としては、プルラン、キサンタガム等を挙げることが出来る。その他、動植物性タンパク質水溶性高分子としてはカゼイン、ゼラチン、大豆タンパク質、小麦グ



ルテン等を挙げることが出来る。

これらの天然水溶性多糖類は、単独あるいは、数種類の物を配合して用いることが出来る。好ましくは、表面張力の調整作用を有するもの同士の組合せである。天然水溶性高分子の使用量は、親水性物質の濃度及び添加量および内容物の流動性によって決められる。

親水性物質と天然水溶性高分子等によつて得られたゲル組成物の粘度が３０℃で１０００センチポイズ以上になる様に天然水溶高分子を添加することが好ましい。

ゲル組成物の粘度が１０００センチポイズ以下になる様な天然水溶性多糖類の添加量では、軟カプセル皮膜剤に充填した時、水分の移行が起こりやすいため好ましくない。

本発明の親水性物質としては、甘草エキスを必須成分として、その他親水性物質を複合することも出来る。

必須成分である甘草エキスは、グリチルレチン酸などのトリテルペン類及びフラボノイド類を含有している水溶性エキスが特に好ましい。

甘草成分であるグリチルレチン酸等の有効成分を分離精製された物であつても良い。

甘草エキスの使用量は、他の配合成分や甘草エキス成分によつて異なり特に限定されないが、グリチルレチン酸誘導体が0.01重量%以上含有することが好ましい。

本発明の親水性物質としては、薬用植物、果汁、魚介類等の抽出エキスまたはその粉末、薬剤、生ローヤルゼリー等を挙げることが出来る。

該天然水溶性高分子に有機酸またはその塩を配合することは、内容物の安定化、ゲル化促進作用等のために添加される。その例として、クエン酸、リンゴ酸、酒石酸、フマル酸、食用酢やかんきつ系果汁等またはその塩を挙げることが出来る。また、無機酸またはその塩（例えばリン酸、リン酸三ナトリウム等）も使用することが出来るが、先に記載した理由により添加することは好ましくない。

有機酸及びまたはその塩の使用量はカプセル内

容物を安定化させる量であり特に限定されない。好ましくは、カプセル内容物のＰＨが1.7～3.6に成る様な量である。

有機酸及びまたはその塩の添加方法は天然水溶性高分子と同時に添加することが出来る。

本発明の天然油は、親水性物質等に含有ないし付着している水分がカプセル皮膜剤面に移行しないように油相を形成するために添加される。また、天然油が持つ整理、栄養効果も併有するために配合する。天然油としては、動物油，植物油，動植物由来の油である。植物油としては紅花油，サンフラワー油，月見草油，ヤシ油，大豆油，オリーブ油，ホホバ油，アボガド油，小麦胚芽油等であり、動物油として、スクワレン，スッポン油，ミンク油，ウナギ油等であり、動植物由来の油としてリノレイン酸，リノール酸，エイコペンクエン酸，ドコサヘキサエン酸等を挙げることが出来る。好ましくは、低温で結晶が析出しない様な天然油単独ないし数種類配合することができる。天然油の使用量は、カプセル内容物の重量に対して２％以上で好ましくは３０～６０重量％である。添加量が２重量％以下では製品の安定性が良くなく水分の移行が起こりやすいためカプセル皮膜剤を溶解したり変形するため好ましくない。

更に内容物は本発明の目的を損なわない範囲で他の添加物、例えば、栄養強化等にビタミン類、着色剤、酸化防止剤等を添加するのは任意である。

本発明に使用する軟カプセル皮膜剤は、特に限定されないが好ましいものはゼラチンである。通常ゼラチンの使用量は、カプセル皮膜剤総重量の５０～８０重量％である。カプセル皮膜剤の製造法は通常の成形法で作ることが出来る。

軟カプセル皮膜剤にカプセル内容物を充填する方法は特に限定されない。常法の浸漬法、打抜き法、滴下法等で製造することが出来る。

［実施例］

以下実施例によつて本発明を更にくわしく説明する。本発明は、これらの実施例によつて限定されるものではない。

実施例１



甘草エキス７部、杜仲エキス１５部、人参エキス５部、精製水１８部を混合し、この溶液にアラビアガム２部、プルラン６部、デキストリン１２部とクエン酸2.5部を加え均一に分散する。この分散液を６５℃に加温し溶解する。この溶解液の中にの６５℃に加温した月見草油４５部を少量ずつ添加し均一になるまで撹拌しカプセル内容物とする。

一方、精製ゼラチン５０部、ソルビトール１５部、精製水６０部を加えて吸水膨潤させ、８０℃に加熱し均一に溶解させ、カプセル皮膜剤を得る。カプセル皮膜剤に先に調整したカプセル内容物を用いてロータリー式打抜き法により充填成型し軟カプセル剤を得た。

軟カプセル剤の内容物として４００mgで皮膜剤１１０mgであつた。

実施例２

実施例１においてデキストリンを微結晶セルローズ１1.5部、タマリンドウ多類体0.5部に変え、月見草油４５部に天然ビタミンＥ0.5部を用いた



他は、実施例１と同様にして本発明の軟カプセル剤を得た。

実施例３

実施例１において月見草油を小麦胚芽油２０部、エイコサンペンクエン酸２５部、天然ビタミンＥ0.5部に変えた他は実施例１と同様に本発明の軟カプセル剤を得た。

実施例４

甘草エキス７部、生ローヤルゼリー３５部、精製水１３部を分散混合し、以下実施例１と同様に本発明の軟カプセル剤を得た。

比較例１

実施例１に用いた甘草エキス７部と、クエン酸2.5部を配合しない以外、実施例１と同様に本発明の軟カプセル剤を得た。

比較例２

生ローヤルゼリー３５部、精製水１２部を分散し、この溶液に月見草油４５部とソルビタン脂肪酸エステル2.5部混合物を少量ずつ添加し均一になるまで撹拌しカプセル内容物とする。以下実施

例１と同様に本発明の軟カプセル剤を得た。

以上実施例１～４および比較例１、２の各軟カプセル剤について、カプセル内容物の活性水分量、室温及び４０℃（各々、相対湿度ＲＨ５０％、経時変化を２ケ月間）調べた結果を付表１に示す。

付表　１

| | 充填物の含水量田量％[1)] | 経時変化 | |
|---|---|---|---|
| | | 室温、２ケ月 | 40℃、２ケ月 |
| 実施例１ | 14.3% | 変化なし | 変化なし |
| 2 | 14.1% | 変化なし | 変化なし |
| 3 | 13.8% | 変化なし | 変化なし |
| 4 | 11.5% | 変化なし | 変化なし |
| 比較例１ | 13.6% | 一部カプセルが変形 | 完全に変形し一部 |
| 2 | 18.9% | 変化なし | カプセルが崩壊 |

1）カールフィッシャー法





［発明の効果］

本発明による軟カプセル剤は親水性物質の軟カプセル剤皮膜剤に充填することが可能になり、熱に不安定な水溶性物質等にも応用範囲を広くする効果がある。さらに本発明はすべて天然物ないし天然由来の原材料を用いたことで市場ニーズを満足させることのできる軟カプセル剤である。

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## SPECIFICATION

1. Title of the invention: Soft Capsule

2. Claims

1) A soft capsule, produced by blending a natural water-soluble high polymer and a hydrophilic substance in natural oil.

2) The soft capsule according to claim 1, which has Glycyrrhizae radix extract as an essential component of the hydrophilic substance.

3) The soft capsule according to claim 1, wherein the natural oil is selected from animal oil, vegetable oil or oil derived from animal or vegetable oil.

4) The soft capsule according to claim 1, wherein an organic acid and/or salt thereof is blended with said natural water-soluble high polymer.

3. Detailed description of the invention

[Field of industrial utilization]

The present invention offers a soft capsule that is composed of natural substances and does not employ synthetic preservatives or synthetic emulsifiers of any kind, which is useful in the pharmaceutical and foodstuff fields for containing substances that are strongly hydrophilic.

[Prior art] In the past, with pharmaceutical products, cosmetics, foodstuffs, and other such products, various substances in forms such as liquids, pastes, suspensions and powders have been introduced into capsules, or have been coated and molded with capsule base to produce capsules. When strongly hygroscopic or hydrophilic substance have been introduced into capsules, synthetic emulsifiers have been added.

[Problems to be solved by the invention]

There are, however, restrictions on capsule contents that can be introduced into soft capsules. It is difficult to introduce plant extracts or drugs that are hydrophilic or hygroscopic into soft capsules.

Specifically, soft capsule coatings (bases) generally have water-soluble gelatin as a primary component, making it difficult to introduce the capsule content due to dissolution or softening of the capsule coating. Specifically, when a strongly hydrophilic substance is to be introduced into a soft capsule, the water content in the content itself is transferred to the capsule coating agent, leading to modifications whereby the capsule coating agent is dissolved. Even if the water content of the hydrophilic substance, etc. is removed, the soft capsule coating will soften due to water content that permeates through the soft capsule coating agent, making it necessary to increase the thickness of the capsule coating agent. When substances such as hydrophilic substances are to be introduced into soft capsules, it is thus necessary to increase the solids content of the capsule coating agent in order to prevent elution of the content by using, for example, wheat germ oil.

When the solids content of the capsule content is increased, the fluidity of the content during packing decreases, making operations difficult.

For these reasons, the manufacturing costs of the soft capsule increase, and the disintegration properties of the capsule are compromised due to the thickening of the capsule coating agent.

In addition, when hydrophilic or other such substances are introduced into soft capsule coating agents, synthetic emulsifiers (surfactants) such as glycerin fatty acid ester, propylene glycol fatty acid ester or sorbitan fatty acid ester are used in order to emulsify or disperse the oil component in the hydrophilic or other such substance. The current state of society places an emphasis on healthful and natural products, and the use of these emulsifiers is not consistent with the current philosophy.

[Means for solving the problems]

As a result of various investigations regarding means for achieving the aforementioned objectives, the present invention was perfected upon discovering that a soft capsule that does not undergo modification or dissolution of the capsule coating agent is produced by blending in a natural oil component with a composition produced by dispersing and dissolving a natural hydrophilic high polymer material in a hydrophilic substance.

Glycyrrhizae radix extract is used as an essential component of the hydrophilic substance, and by blending in natural water-soluble polysaccharide and organic acid or salt thereof with this substance, a gel composition is obtained that has excellent fluidity, and does not allow transport of water content. A natural oil component is added to this gel composition, and the emulsified composition is then introduced into the soft capsule coating agent.

The natural water-soluble high polymer material of the present invention has no particular restrictions, provided it is a substance that has a gelling, thickening or stabilization action.

Examples of substances that can be cited include seaweed binders such as carrageenan, *fua-seran**, agar and alginate, vegetable water-soluble high polymers such as

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* phonetic spelling—Trans. Note.

guar gum, tamarind, locust bean gum, gum arabic, pectin, starch, dextrin and konnyaku mannan, and viscous high polymer materials derived from microorganisms, such as pullulan and xanthan gum. In addition, examples of animal and vegetable protein water-soluble high polymers that can be cited include casein, gelatin, soy protein and wheat gluten.

These natural water-soluble polysaccharides can be used individually or multiple types can be blended together, and it is preferable to combine substances that have a surface-tension conditioning effect. The amount of natural water-soluble high polymer material which is used is to be determined in accordance with the concentration and added amount of hydrophilic substance, and the fluidity of the content.

It is preferable to add the natural water-soluble high polymer material so that the viscosity of the gel composition that is obtained from the hydrophilic substance and natural water-soluble high polymer material is 1000 cp or greater at 30°C.

If the added amount of natural water-soluble polysaccharide is such that the viscosity of the gel composition is less than 1000 cp, then transfer of water content will tend to occur when the material is introduced into the soft capsule coating agent.

Glycyrrhizae radix extract is an essential component of the hydrophilic substance of the present invention, and other hydrophilic substances can also be combined.

It is particularly desirable for the essential component of Glycyrrhizae radix extract to be a water-soluble extract that contains flavonoids and triterpenes such as glycyrrhetic acid.

The glycyrrhetic acid which is an effective component in the Glycyrrhizae radix can be a substance that has been separated and purified.

There are no particular restrictions on the amount of Glycyrrhizae radix extract used, as amounts will differ depending on the other blended components and the components of the Glycyrrhizae radix. It is preferable, however, for glycyrrhetic acid derivatives to be present in an amount of 0.01 wt% or greater.

Examples of the hydrophilic substance of the present invention that can be cited include extracts and extract powders obtained from medicinal plants, fruit juices or seafood, as well as drugs, and raw royal jelly.

Blending organic acids or salts thereof with said natural water-soluble high polymer material has the action of stabilizing the contents and accelerating gelation. Examples that can be cited include citric acid, malic acid, tartaric acid, fumaric acid, vinegar, citrus fruit juices, and salts thereof. In addition, inorganic acids and salts thereof (e.g., phosphoric acid, trisodium phosphate) may also be used, but adding such substances is undesirable for the reasons discussed previously.

The amount of organic acid or salt thereof which is used has no particular restrictions, as an amount is used that allows stabilization of the capsule content. Preferably, an amount is used that adjusts the pH of the capsule content to 1.7-3.6.

The method for adding the organic acid and/or salt can involve addition at the same time as the natural water-soluble high polymer material.

The natural oil of the present invention is added in order to form an oil phase so that water content contained or affixed to the hydrophilic substance is not transferred to the surface of the capsule coating agent. In addition, such substances can also be blended in order to provide the pharmacological or nutritive effects possessed by the natural oil. Examples of natural oils that can be cited are animal oils, vegetable oils and oils derived from animal and vegetable oils. Examples of vegetable oils that can be cited include safflower oil, sunflower oil, evening primrose oil, coconut oil, soy oil, olive oil, jojoba oil, avocado oil and wheat germ oil. Examples of animal oils include squalene, mud turtle oil, mink oil and eel oil. Examples of oils derived from animal and vegetable oils include linolenic acid, linoleic acid, eicosapentaenoic acid and docosahexaenoic acid. It is preferable for a single natural oil to be used, but multiple types may be blended in such a manner that crystals do not precipitate at low temperatures. The amount of natural oil which is used is 2% or greater with respect to the weight of the capsule content, with 30-60 wt% being preferred. If the added amount is less than 2 wt%, the stability of the product will be poor, and water transfer will tend to occur, resulting in dissolution or modification of the capsule coating.

In addition, other additives such as vitamins for nutrient enrichment, as well as colorants and antioxidants, can also be added as desired in ranges in which the objectives of the present invention are not compromised.

The soft capsule coating agent used in the present invention has no particular restrictions, but gelatin is preferred. The amount of gelatin used is ordinarily 50-80 wt% of the total weight of the capsule coating agent. The method for manufacturing the capsule coating agent can be a common molding method.

There are no particular restrictions on the method for introducing the capsule content into the soft capsule coating agent, and manufacture can be carried out by methods such as common dipping methods, stamping methods and dripping methods.

[Working examples]

The present invention is described in additional detail below using working examples, but the present invention is not restricted to these working examples.

Working Example 1

Seven parts of Glycyrrhizae radix extract, 15 parts of Eucommia extract, 5 parts of ginseng extract and 18 parts of purified water were mixed, whereupon 2 parts of gum arabic, 6 parts of pullulan, 12 parts of dextrin and 2.5 parts of citric acid were added to this solution, and dispersed until uniform. This dispersion was then heated to 65°C to effect dissolution, 45 parts of evening primrose oil heated to 65°C were added in small quantities, and the mixture was stirred until uniform to produce the capsule content.

Meanwhile, 50 parts of purified gelatin, 15 parts of sorbitol, and 60 parts of purified water were added. The water was absorbed and swelling occurred, whereupon the material was heated to 80°C and the materials were uniformly dissolved to produce the capsule coating agent. A rotary stamping method was carried out using the prepared capsule content which was introduced and molded into the capsule coating agent, thus producing the soft capsules.

The soft capsule content weighed 400 mg, and the coating agent weighed 110 mg.

Working Example 2

The soft capsule of the present invention was produced in the same manner as in Working Example 1, with the exception that the dextrin was substituted by 11.5 parts of

microcrystalline cellulose, and that 0.5 part of tamarind *taruitai*[*] and 0.5 part of natural vitamin E was used in the 45 parts of evening primrose oil.

Working Example 3

The soft capsule of the present invention was produced in the same manner as in Working Example 1, with the exception that the evening primrose oil in Working Example 1 was substituted by 20 parts of wheat germ oil, 25 parts of eicosapentaenoic acid and 0.5 part of natural vitamin E.

Working Example 4

The soft capsule of the present invention was produced in the same manner as in Working Example 1, with the exception that 7 parts of Glycyrrhizae radix extract, 35 parts of raw royal jelly and 13 parts of purified water were dispersed and blended.

Comparative Example 1

The soft capsule of the present invention[**] was produced in the same manner as in Working Example 1, with the exception that the 7 parts of Glycyrrhizae radix extract and 2.5 parts of citric acid used in Working Example 1 were not blended in.

Comparative Example 2

Thirty-five parts of raw royal jelly and 12 parts of purified water were dispersed together, and a mixture of 45 parts of evening primrose oil and 2.5 parts of sorbitan fatty acid ester was added in small quantities to this solution. The materials were then stirred until uniform to produce the capsule content. The soft capsule of the present invention[**] was then obtained in the same manner as in Working Example 1.

Regarding the soft capsules of Working Examples 1-4 and Comparative Examples 1 and 2, results are presented in regard to the active water content present in the capsule

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[*] This may be a misprint for polysaccharide—Trans. Note.

[**] sic; Comparative Example?—Trans. Note.

content and the effect when stored at room temperature and 40°C (50% relative humidity (RH), change over 2 months).

Table 1

| Water content of introduced material wt% [1)] | | Change over time | |
|---|---|---|---|
| | | Room temperature, 2 months | 40°C, 2 months |
| Working Example 1 | 14.3% | No change | No change |
| Working Example 2 | 14.1% | No change | No change |
| Working Example 3 | 13.8% | No change | No change |
| Working Example 4 | 11.5% | No change | No change |
| Comparative Example 1 | 13.6% | Partial capsule deformation | Completely deformed in parts |
| Comparative Example 2 | 18.9% | No modification | Disintegration of capsule |

1) Carl Fischer method

[Effect of the invention]

The soft capsule of the present invention allows introducing hydrophilic material into a soft capsule coating agent, and has the effect of expanding the range of utilization of the technology to accommodate water-soluble substances that are not stable with respect to heat. Moreover, the present invention also offers a soft capsule that satisfies market demands due to the use of completely natural substances, or substances that are derived from natural raw materials.